



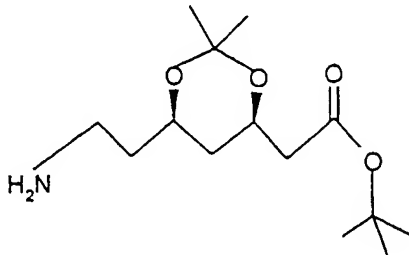
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

BE

(51) International Patent Classification ⁷ : C07D 319/06	A1	(11) International Publication Number: WO 00/68221 (43) International Publication Date: 16 November 2000 (16.11.00)
<p>(21) International Application Number: PCT/HU00/00042</p> <p>(22) International Filing Date: 5 May 2000 (05.05.00)</p> <p>(30) Priority Data: P9901526 6 May 1999 (06.05.99) HU</p> <p>(71) Applicant (for all designated States except US): EGIS GYÓGYSZERGYÁR RT. [HU/HU]; Keresztúri út 30-38, H-1106 Budapest (HU).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): KÓTAY NAGY, Péter [HU/HU]; Nagymező u. 73, H-2600 Vác (HU). GR- EFF, Zoltán [HU/HU]; Gyöngyvirág u. 8, H-1028 Bu- dapest (HU). BARKÓCZY, József [HU/HU]; Szirom u. 4-6/B, H-1016 Budapest (HU). SIMIG, Gyula [HU/HU]; Hollósy S. u. 25, H-1126 Budapest (HU). BALÁZS, László [HU/HU]; Baross u. 38, H-1088 Budapest (HU). DOMÁN, Imre [HU/HU]; Mohács u. 18/B, H-1035 Bu- dapest (HU). RATKAI, Zoltán [HU/HU]; Monori u. 19, H-1101 Budapest (HU). SERES, Péter [HU/HU]; Rádda Barnen u. 6, H-1153 Budapest (HU). BARTHA, Ferenc [HU/HU]; Kabay u. 3-5/5, H-4440 Tiszavasvári (HU). VERECZKEYNÉ DONÁTH, Györgyi [HU/HU]; Lajos u.</p>	<p>49/b, H-1036 Budapest (HU). NAGY, Kálmán [HU/HU]; Turista u. 2/a, H-1025 Budapest (HU).</p> <p>(74) Agent: ADVOPATENT; Office Of Patent And Trademark Attorneys, P.O. Box 11, H-1251 Budapest (HU).</p> <p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
(54) Title: SALTS OF 2,2-DIMETHYL-1,3-DIOXANE INTERMEDIATES AND PROCESS FOR THE PREPARATION THEREOF		
(57) Abstract		
<p>The invention relates to salts of (4R-cis)- -(1,1-dimethyl-ethyl)- -6-(2-aminoethyl)- -2,2-dimethyl-1,3-diox- -ane-4-acetate of formula (I) formed with organic acids. The new salts according to the invention are stable and can be easily purified by recrystallization. The new salts of the invention are valuable pharmaceutical intermediates which can be used e.g. in the preparation of the hypolipidemic agent having the generic (INN) name atorvastatin. The invention further relates to the preparation of the new salts of the compound of formula (I).</p>	 <p>(I)</p>	

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SALTS OF 2,2-DIMETHYL-1,3-DIOXANE INTERMEDIATES AND PROCESS FOR THE PREPARATION THEREOF

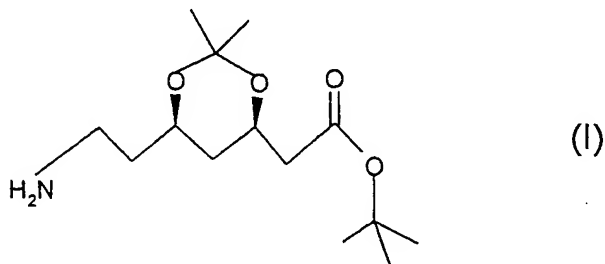
FIELD OF THE INVENTION

This invention relates to new pharmaceutical intermediates and a process for the preparation thereof.

The invention relates more particularly to salts of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate formed with organic acids.

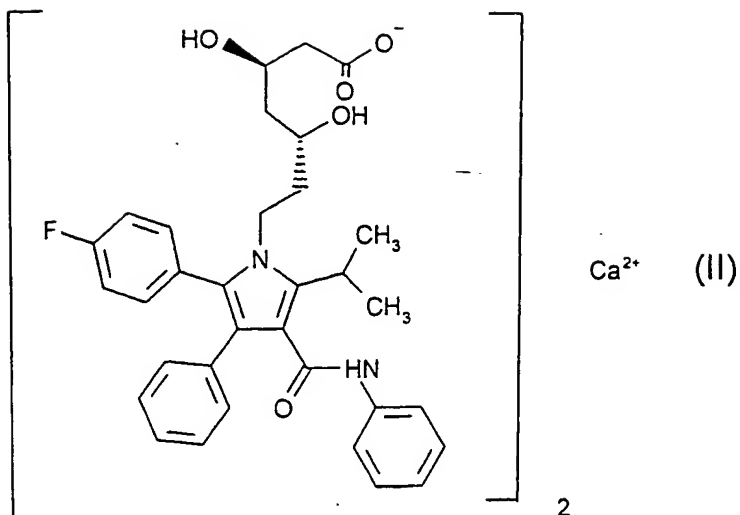
TECHNICAL BACKGROUND

The (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate of the Formula



is a valuable pharmaceutical intermediate which can be used e.g. in the preparation of the hypolipidemic agent of the Formula

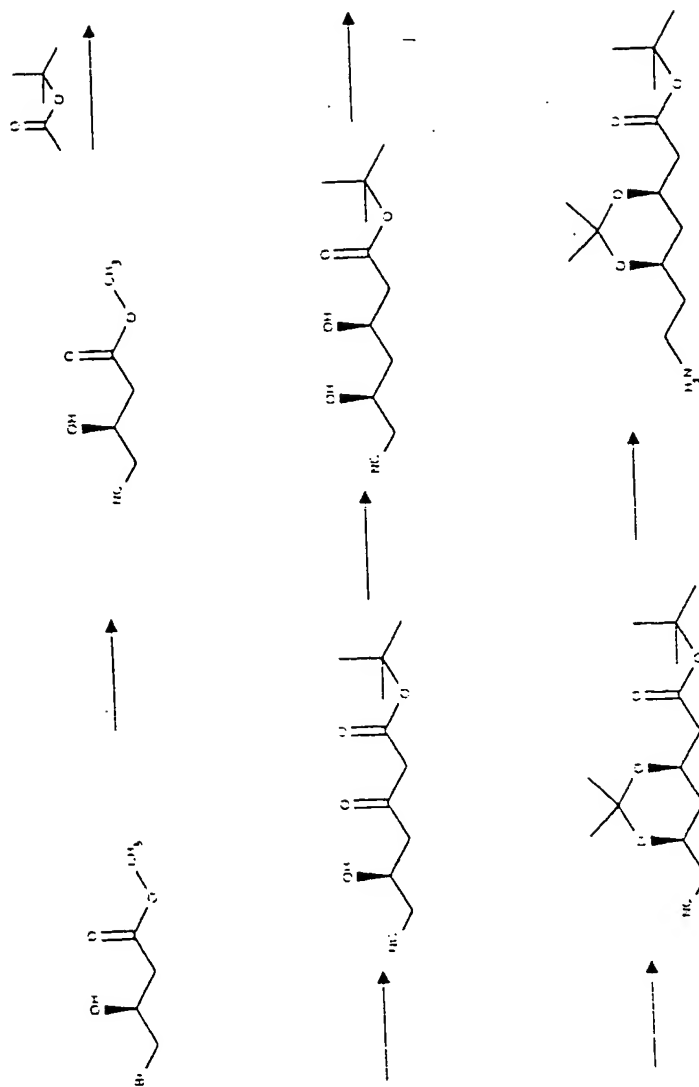
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having the international non-proprietary name (INN) atorvastatin.

Two methods are known from prior art for the preparation of the compound of the Formula I. The process disclosed in US patent No. 5,155,251 is disclosed on reaction scheme A.

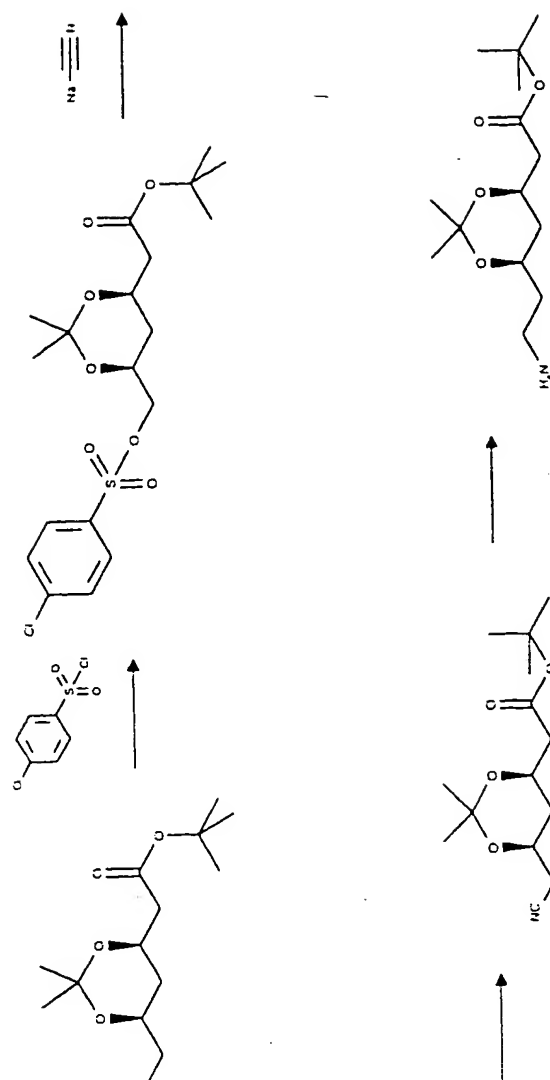
Reaction scheme A



According to this patent the aminoethyl derivative of the Formula I is prepared by fractionated distillation carried out at 125-135°C/0.05 Hgmm. The purity of the product is not higher than 96 %. The disadvantage of this process is that fractionated distillation in high vacuo is a complicated purification method which is only circumstantially feasible on industrial scale.

The process set forth in US patent No. 5,103,024 and the corresponding Hungarian patent No. 213,731 is shown on reaction scheme B.

Reaction scheme B



According to this patent the compound of the Formula I is purified by column chromatography. The drawback of this process is that column chromatography requires large investments and is but difficultly feasible, particularly on industrial scale. The purity of the product obtained does not exceed 98.2 %.

The disadvantage of the above two known processes is that a product having a purity higher than 99 % can be prepared neither by means of fractional distillation nor by column chromatography.

ESSENCE OF THE INVENTION

It is the object of the present invention to overcome the drawbacks of the known processes and to elaborate a simple process for the preparation of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate which is preferably feasible on industrial scale too and provides a product having a purity above 99 %.

The above object is solved by the present invention.

It has been found that (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate of the Formula I forms with organic acids salts which can be excellently crystallized, are stable and of high purity. The invention compound of the Formula I being in salt form is extremely pure and can be advantageously converted into atorvastatin of the Formula II having a purity which meets the requirements of Pharmacopoeia. The advantage of the present invention is that fractionated distillation carried out in high vacuo and

column chromatography used in prior art methods are eliminated.

According to an aspect of the present invention there are provided salts of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate formed with organic acids.

According to a further aspect of the invention there is provided a process for the preparation of salts of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate formed with organic acids which comprises reacting the compound of the Formula I with an organic acid in an organic solvent.

DETAILS OF THE INVENTION

The present invention is based on the recognition that the compound of the Formula I forms stable salts with organic acids. This recognition is so much the more surprising as it is known from prior art that ketales are instable in the presence of acids. The two hydroxy groups of the amine derivative of the Formula I are protected by a ketale ring. It was unforeseen that said ketale group would be resistant to organic acids under the reaction conditions used. It is particularly surprising that the salts of the present invention are not only stable at room temperature but remain stable even during recrystallization from an organic solvent carried out at higher temperature.

According to the process of the present invention the following acids may be used for salt formation: an aliphatic monocarboxylic acid, dicarboxylic acid or polycarboxylic acid,

cycloalkane carboxylic acid, aliphatic unsaturated carboxylic acid, aromatic carboxylic acid, heterocyclic carboxylic acid or sulphononic acid.

According to a preferred embodiment of our invention the following acids are used: acetic acid, butyric acid, valeric acid, isovaleric acid, pivalic acid, oxalic acid, malic acid, succinic acid, malonic acid, citric acid, cyclopropane carboxylic acid, cyclobutane carboxylic acid, cyclopentane carboxylic acid, cyclohexane carboxylic acid, fumaric acid, maleic acid, benzoic acid, m-methyl-benzoic acid, 4-methoxy-benzoic acid, 4-bromo-benzoic acid, 4-tert. butyl-benzoic acid, benzenesulfonic acid, methanesulfonic acid, p-methyl-benzenesulfonic acid, p-bromo-benzenesulfonic acid, nicotic acid, tetrahydrofuran-2-carboxylic acid or tiophen-3-carboxylic acid.

According to a particularly preferred embodiment of our invention pivalic acid is used.

The reaction may be carried out in an apolar, dipolar aprotic or protic solvent. As reaction medium an aliphatic hydrocarbon, aromatic hydrocarbon, halogenated hydrocarbon, ester, nitrile, alcohol or ether may be used. It is preferred to use one of the following solvents: hexane, heptane, petrolether, toluene, benzene, xylene, dichloro methane, chloroform, ethyl acetate, acetonitrile, methanol, ethanol, isopropanol, tetrahydrofuran, dioxane or diethyl ether.

A solvent mixture may also be used as reaction medium. It is preferred to use a mixture of heptane and toluene; hexane

and toluene; hexane, toluene and tetrahydrofurane; heptane, toluene and tetrahydrofurane; or hexane and diethyl ether.

According to a particularly preferred embodiment of our invention the compound of the Formula I and the organic acid are reacted in the form of solutions formed with the same solvent.

It is preferred to use the compound of the Formula I and the organic acid in a molar ratio of 0.5-5, preferably 0.5-2, particularly preferably 0.5-1.2.

The compound of the Formula I and the organic acid are admixed preferably at room temperature and the reaction may be performed under heating or at room temperature. One may preferably work at the boiling point of the reaction mixture.

The reaction mixture may be worked up by simple methods. One may proceed preferably by cooling the reaction mixture, isolating the precipitated salt of the compound of the Formula I by filtration or centrifugation, washing the salt with an organic solvent and drying. The salt may be purified by recrystallization.

According to a preferred embodiment of the process according to the present invention as starting material a crude compound of the Formula I is used. In this case the expensive and complicated purification of the compound of the Formula I is eliminated.

The advantages of the present invention may be summarized as follows:

According to the present invention the compound of the Formula I is purified by simple recrystallization which can be carried out significantly easier than fractionated distillation performed in high vacuo and column-chromatography used in the known methods.

The present invention provides a product of higher purity than the prior art methods. After a single recrystallization step the purity of the product is > 99 % (according to gas chromatography), after two-fold recrystallization the purity amounts to > 99.95 %. The purity of the product obtained by known methods is lower than 98 %.

The process of the present invention can be easily carried out on industrial scale too. The scaling-up causes no problems. On the other hand the fractionated distillation performed in high vacuo and column chromatography requires considerable investments and is but difficultly feasible on industrial scale.

The compound of the Formula I is stable and can be stored for a long period of time without decomposition in the form of salts formed with organic acids.

From the high purity salts of the compound of the Formula I according to the present invention atorvastatin meeting the requirements of Pharmacopoeia can be prepared.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.

Example 1Pivalate of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

55 g of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 500 ml of a 4:1 mixture of heptane and toluene. 20.6 g (201 millimoles) of pivalic acid are dissolved in 190 ml of a 4:1 mixture of heptane and toluene. The two solutions are admixed and the reaction mixture is refluxed for an hour. The hot solution is filtered and the mixture is cooled with icecold water under stirring. The precipitated crystals are filtered, washed with a cold mixture of heptane and toluene and dried. Thus 64.9 g (172 millimoles) of the desired compound are obtained, yield 86 %, mp.: 131°C.

Elementary analysis: for	C%	H%	N%
calc.:	60.77	9.93	3.73
found:	60.77	9.88	3.81

TLC propanol/ammonia = 7:3, R_f = 0.63

IR (KBr): 2949, 1725, 1520, 1173.

¹HNMR (DMSO, δ 400): 4.17 (m, 1H), 3.98 (m, 1H), 2.66 (m, 2H), 2.36 (dd, $J_1=4.9$ Hz, $J_2=15.0$ Hz, 1H), 2.22 (dd, $J_1=8.1$ Hz, $J_2=15.0$ Hz, 1H), 1.54 (m, 3H), 1.39 (s, 12H), 1.24 (s, 3H), 1.05 (s, 9H), 1.03 (~t, $J=12.0$ Hz, 1H).

¹³CNMR: 180.87, 169.77, 98.22, 79.85, 66.50, 66.12, 42.34, 38.26, 37.05, 36.44, 35.97, 30.11, 28.03, 27.92, 19.88.

MS: 274 (3), 202 (57), 200 (47), 173 (44), 158 (50), 57 (100), 41 (48), 30 (96).

GC content > 99%, diastereomer contamination < 0.7%.

Example 2

Pivalic acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

23.3 g of one recrystallized (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate pivalic acid salt are dissolved in 220 ml of a 4:1 mixture of hexane and toluene. The solution is heated to reflux, the hot solution is filtered and the mixture is cooled with icecold water under stirring. The precipitated crystals are filtered, washed with cold diethyl ether and dried. Thus 20.7 g of the desired product are obtained, yield 89 %, mp.: 132-133°C.

GC content > 99.95 %; total impurities < 0.05 %.

Example 3

Pivalic acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

21 g of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 116 ml of a 2:2:1 mixture of hexane, toluene and tetrahydrofurane. 7.6 g (201 millimoles) of pivalic acid are dissolved in 53 ml of a 1:1 mixture of hexane and toluene. The two solutions are admixed and the reaction mixture is heated to boiling under reflux. The hot solution is filtered and the mixture is cooled with icecold water under stirring. The precipitated crystals are filtered, washed with cold diethyl ether and dried. Thus 21.1 g of the desired product are obtained. Yield 73 %, mp.: 131°C.

Example 4

Pivalic acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

24 g (87.8 millimoles) of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 200 ml of a 4:1:1 mixture of heptane, toluene and tetrahydrofurane. 9.0 g (88 millimoles) of pivalic acid are dissolved in 100 ml of a 4:1:1 mixture of heptane, toluene and tetrahydrofurane. The two solutions are admixed and the reaction mixture is heated to boiling under reflux. The hot solution is filtered and the mixture is cooled with icecold water under stirring. The precipitated crystals are filtered, washed with cold diethyl ether and dried. Thus 29.0 g of the desired compound are obtained, yield 88 %, mp.: 131°C.

Example 5

Benzoic acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

0.6 g (219 millimoles) of crude (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 4 ml of ethyl acetate. 0.26 g of benzoic acid are dissolved in 8 ml of a 1:1 mixture of hexane and diethyl ether. The two solutions are admixed and stirred at room temperature for an hour. The reaction mixture is evaporated in vacuo. The residue is recrystallized from 5 ml of a 4:1 mixture of hexane and toluene. After cooling the precipitated crystals are filtered, washed with cold hexane and dried. Thus 0.71 g

of the desired compound are obtained, yield 82 %, mp.: 113-114°C.

Formula: $C_{21}H_{33}NO_6$

Molecular weight: 395.500

Elementary analysis: for	C%	H%	N%
calc.:	63.78	8.41	3.54
found:	63.74	8.38	3.55

TLC propanol/ammonia = 7:3 R_f = 0.63

IR (KBr): 2979, 1722, 1519, 1370.

¹H NMR (CDCl₃, g200): 8.39 (b, 3H), 7.98 (~d, J=7.0 Hz, 2H), 7.39 (m, 3H), 4.13 (m, 1H), 3.79 (m, 1H), 2.97 (m, 2H), 2.23 (m, 2H), 1.70 (m, 2H), 1.43 (s, 9H), 1.32 (s, 3H), 1.27 (s, 3H), 1.00 (m, 2H).

Example 6

Maleic acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

0.6 g (219 millimoles) of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 6 ml of diethyl ether. 0.25 g (219 millimoles) of maleic acid are dissolved in 4 ml of diethyl ether. The two solutions are admixed and stirred at room temperature. After cooling the precipitated crystals are filtered, washed with cold hexane and dried. Thus 0.80 g of the desired compound are obtained, yield 93 %, mp.: 87-89°C.

Formula: $C_{18}H_{31}NO_8$

Molecular weight: 389.450

Elementary analysis: for	C%	H%	N%
calc.:	55.51	8.02	3.60
found:	54.70	8.12	3.52

TLC propanol/ammonia =7:3 R_f =0.63.

IR (KBr):3430, 2980, 1722.

¹HNMR (CDCl₃, i400): 7.97 (b, 3H), 6.25 (s, 2H), 4.28 (m, 1H), 4.10 (m, 1H), 3.21 (m, 2H), 2.40 (m, 1H), 2.31 (m, 1H), 1.89 (m, 2H), 1.57 (m, 1H), 1.46 (s, 3H), 1.44 (s, 9H), 1.35 (s, 3H), 1.27 (m, 1H).

Example 7

Fumaric acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

0.6 g (219 millimoles) of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 4 ml of anhydrous ethanol. 0.25 g (219 millimoles) of fumaric acid are dissolved in 10 ml of anhydrous ethanol. The two solutions are admixed and stirred at room temperature. The reaction mixture is evaporated and the residue is suspended in hexane. After cooling the precipitated crystals are filtered and recrystallized from 2-propanol. Thus 0.75 g of the desired compound are obtained, yield 85 %, mp.: 145-148°C.

Formula: C₁₈H₃₁NO₈

Molecular weight: 389.450

Elementary analysis: for	C%	H%	N%
calc.:	55.51	8.02	3.60
found:	55.31	8.04	3.55

TLC propanol/ammonia =7:3 R_f =0.63

IR (KBr): 3430, 2988, 1736, 1157.

¹H NMR (DMSO, g200): 8.52 (b, 3H), 6.44 (s, 2H), 4.17 (m, 1H), 3.98 (m, 1H), 2.80 (m, 2H), 2.36 (m, 1H), 2.19 (m, 1H), 1.68 (m, 2H), 1.58 (m, 1H), 1.38 (m, 12H), 1.24 (m, 3H), 1.09 (m, 1H).

Example 8

Meta-methyl-benzoic acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

0.6 g (219 millimoles) of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 6 ml of diethyl ether. 0.3 g (219 millimoles) of meta-methyl-benzoic acid are dissolved in 3 ml of diethyl ether. The two solutions are admixed and stirred at room temperature. The reaction mixture is evaporated and the residue is crystallized from a 5:1 mixture of hexane and toluene. Thus 0.84 g of the desired compound are obtained, yield 92 %, mp.: 95-96°C.

Formula: C₂₂H₃₅NO₆

Molecular weight: 409.527

Elementary analysis: for	C%	H%	N%
calc.:	64.52	8.61	3.42
found:	64.23	8.64	3.45

TLC propanol/ammonia =7:3 R_f =0.63

IR (KBr): 2977, 2200, 1722, 1367.

¹H NMR (CDCl₃, i400): 8.86 (b, 3H), 7.79 (m, 1H), 7.77 (m, 1H), 7.24 (m, 2H), 4.13 (m, 1H), 3.79 (m, 1H), 3.02 (m, 1H), 2.93

(m, 1H), 2.37 (s, 3H), 2.31 (m, 1H), 2.18 (m, 1H), 1.71 (m, 2H), 1.50 (m, 1H), 1.43 (s, 9H), 1.33 (s, 3H), 1.26 (s, 3H), 1.00 (m, 1H).

Example 9

Benzenesulfonic acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

0.6 g (219 millimoles) of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 5 ml of a 4:1 mixture of hexane and toluene. 0.34 g (219 millimoles) of benzenesulfonic acid are dissolved in 5 ml of toluene. The two solutions are admixed. The reaction mixture is stirred at room temperature and evaporated in vacuo. The residue is recrystallized from a 5:1 mixture of hexane and toluene. Thus 0.76 g of the desired compound are obtained, yield 80 %, mp.: 96-98°C.

Formula: $C_{20}H_{33}NO_7S$

Molecular weight: 431.553

Elementary analysis:

for	C%	H%	S%	N%
calc.:	55.66	7.71	7.43	3.25
found:	54.79	7.73	7.32	3.28

TLC propanol/ammonia =7:3 R_f =0.63

IR (KBr): 3430, 2976, 1737, 1719, 1165.

¹H NMR (CDCl₃, 400): 7.90 (m, 1H), 7.63 (m, 2H), 7.40 (m, 2H), 4.13 (m, 1H), 3.82 (m, 1H), 2.98 (m, 2H), 2.33 (m, 1H), 3.21 (m, 1H), 1.68 (m, 2H), 1.50 (m, 1H), 1.44 (s, 9H), 1.33 (s, 3H), 1.27 (s, 3H), 1.03 (m, 1H).

Example 10

Acetic acid salt of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

0.6 g (219 millimoles) of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 6 ml of diethyl ether. 0.131 g (219 millimoles) of acetic acid are dissolved in 5 ml of diethyl ether. The two solutions are admixed. The reaction mixture is stirred at room temperature. The crystals are filtered, washed with hexane and dried at room temperature in vacuo. Thus 0.56 g of the desired compound are obtained, yield 76 %, mp.: 76-77°C.

Formula: $C_{16}H_{31}NO_6$

Molecular weight: 333.429

Elementary analysis: for	C%	H%	N%
calc.:	57.64	9.37	4.20
found:	57.80	9.40	4.09

TLC propanol/ammonia =7:3 R_f =0.63

IR (KBr): 3430, 2986, 1731, 1157.

¹H NMR (CDCl₃, 400): 8.18 (b, 3H), 4.26 (m, 1H), 3.97 (m, 1H), 2.93 (m, 2H), 2.43 (m, 1H), 2.29 (m, 1H), 1.96 (s, 3H), 1.80 (m, 2H), 1.56 (m, 1H), 1.44 (s, 9H), 1.44 (s, 3H), 1.34 (s, 3H), 1.22 (m, 1H).

Example 11**Bis-(4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate oxalic acid salt**

0.6 g (219 millimoles) of crude oily (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate are dissolved in 6 ml of diethyl ether. 0.19 g (219 millimoles) of oxalic acid are dissolved in 3 ml of diethyl ether. The two solutions are admixed. The reaction mixture is stirred at room temperature. The precipitated crystals are filtered, washed with cold hexane and dried at room temperature in vacuo. Thus 0.56 g of the desired compound are obtained, yield 80 %, mp.: 76-77°C.

Formula: $C_{30}H_{56}N_2O_{12}$

Molecular weight: 333.429

Elementary analysis: for	C%	H%	N%
calc.:	56.59	8.86	4.40
found:	56.21	8.38	4.36

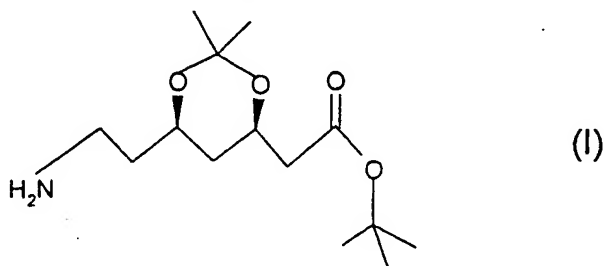
TLC propanol/ammonia =7:3 R_F =0.63

IR (KBr): 3430, 2982, 1739, 1575, 1161.

HNMR ($CDCl_3$, 400): 8.60 (b, 3H), 4.24 (m, 1H), 3.99 (m, 1H), 3.00 (m, 2H), 2.32 (m, 2H), 1.90 (m, 2H), 1.54 (m, 1H), 1.44 (s, 9H), 1.41 (s, 3H), 1.32 (s, 3H), 1.21 (m, 1H).

What we claim is,

1. Salts of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-amino-ethyl)-2,2-dimethyl-1,3-dioxane-4-acetate of the Formula



formed with organic acids.

2. Salts of the compound of the Formula I according to Claim 1 formed with an aliphatic monocarboxylic acid, dicarboxylic acid or polycarboxylic acid, cycloalkane carboxylic acid, aliphatic unsaturated carboxylic acid, aromatic carboxylic acid, heterocyclic carboxylic acid or sulphonic acid.

3. Salts of the compound of the Formula I according to Claim 2 formed with acetic acid, butyric acid, valeric acid, isovaleric acid, pivalic acid, oxalic acid, malic acid, succinic acid, malonic acid, citric acid, cyclopropane carboxylic acid, cyclobutane carboxylic acid, cyclopentane carboxylic acid, cyclohexane carboxylic acid, fumaric acid, maleic acid, benzoic acid, m-methyl-benzoic acid, 4-methoxy-benzoic acid, 4-bromo-benzoic acid, 4-tert. butyl-benzoic acid, benzenesulfonic acid, methanesulfonic acid, p-methyl-benzenesulfonic acid, p-bromo-benzenesulfonic acid, nicotic

acid, tetrahydrofuran-2-carboxylic acid or tiophen-3-carboxylic acid.

4. Salt of the compound of the Formula I according to Claim 1 formed with pivalic acid.

5. Process for the preparation of salts of (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate of the Formula I which comprises reacting (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate of the Formula I with an organic acid in an organic solvent.

6. Process according to Claim 5 which comprises using as organic acid an aliphatic monocarboxylic acid, dicarboxylic acid or polycarboxylic acid, cycloalkane carboxylic acid, aliphatic unsaturated carboxylic acid, aromatic carboxylic acid, heterocyclic carboxylic acid or sulphonic acid.

7. Process according to Claim 6 which comprises using acetic acid, butyric acid, valeric acid, isovaleric acid, pivalic acid, oxalic acid, malic acid, succinic acid, malonic acid, citric acid, cyclopropane carboxylic acid, cyclobutane carboxylic acid, cyclopentane carboxylic acid, cyclohexane carboxylic acid, fumaric acid, maleic acid, benzoic acid, m-methyl-benzoic acid, 4-methoxy-benzoic acid, 4-bromo-benzoic acid, 4-tert. butyl-benzoic acid, benzenesulfonic acid, methanesulfonic acid, p-methyl-benzenesulfonic acid, p-bromo-benzenesulfonic acid, nicotic acid, tetrahydrofuran-2-carboxylic acid or tiophen-3-carboxylic acid.

8. Process according to Claim 7 which comprises using pivalic acid.

9. Process according to any of Claims 6-8 which comprises using as reaction medium an apolar, dipolar, aprotic or protic solvent.

10. Process according to Claim 9 which comprises using as organic solvent an aliphatic hydrocarbon, aromatic hydrocarbon, halogenated hydrocarbon, ester, nitrile, alcohol or ether.

11. Process according to Claim 10 which comprises using as organic solvent hexane, heptane, petrolether, toluene, benzene, xylene, dichloro methane, chloroform, ethyl acetate, acetonitrile, methanol, ethanol, isopropanol, tetrahydrofurane, dioxane or diethyl ether.

12. Process according to any of Claims 9-11 which comprises using as reaction medium a solvent mixture.

13. Process according to Claim 12 which comprises using as reaction medium a mixture of heptane and toluene; hexane and toluene; hexane, toluene and tetrahydrofurane; heptane, toluene and tetrahydrofurane; or hexane and diethyl ether.

14. Process according to any of Claims 5-13 which comprises dissolving the compound of the Formula I and the organic acid in the same solvent and admixing the two solutions.

15. Process according to any of Claims 5-14 which comprises using the compound of the Formula I and the

organic acid in a molar ratio of 0.5-5, preferably 0.5-2, particularly preferably 0.5-1.2.

16. Process according to any of Claims 5-15 which comprises carrying out the reaction at room temperature or under warming, preferably at 20-90°C.

17. Process according to any of Claims 5-16 which comprises using as starting material crude (4R-cis)-(1,1-dimethyl-ethyl)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate.

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.
PCT/HU 0042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D319/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 155 251 A (BUTLER DONALD E ET AL) 13 October 1992 (1992-10-13) cited in the application example 3	1-17
Y	WO 92 06968 A (WARNER LAMBERT CO) 30 April 1992 (1992-04-30) cited in the application example 2	1-17
Y	EP 0 330 172 A (WARNER LAMBERT CO) 30 August 1989 (1989-08-30) *formulae IVb, XXI, XXIIIa* claim 35; examples 1-3	1-17

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

29 August 2000

Date of mailing of the international search report

12/09/2000

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/HU/0042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" TETRAHEDRON LETTERS, NL, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 33, no. 17, 21 April 1992 (1992-04-21), pages 2283-2284, XP000608147 ISSN: 0040-4039 example 6	1-17
Y	US 5 599 954 A (MITSUHASHI SIGERU ET AL) 4 February 1997 (1997-02-04) reference example 3	1-17
Y	WO 98 04543 A (WARNER LAMBERT CO ; BUTLER DONALD EUGENE (US); JACKS THOMAS ELLIOTT) 5 February 1998 (1998-02-05) example 6	1-17
P, Y	WO 99 57109 A (INOUE KENJI ; MITSUDA MASARU (JP); MIYAZAKI MAKOTO (JP); KANEGAFUCH) 11 November 1999 (1999-11-11) claims 1,4	1-17
A	US 5 278 313 A (THOTTATHIL JOHN K ET AL) 11 January 1994 (1994-01-11) column 7, line 14 - line 54	1-17
A	REESE C B: "PROTECTIVE GROUPS IN ORGANIC CHEMISTRY: PROTECTION OF GLYCOL SYSTEMS", PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, PAGES 120-143 XP002042278 page 122, paragraph 1	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HU/00042

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5155251 A	13-10-1992	AT 175190 T	15-01-1999
		AU 667320 B	21-03-1996
		AU 2764192 A	03-05-1993
		CA 2116973 A	15-04-1993
		DE 69228073 D	11-02-1999
		DE 69228073 T	10-06-1999
		EP 0643689 A	22-03-1995
		ES 2129457 T	16-06-1999
		FI 941632 A	08-04-1994
		JP 7500105 T	05-01-1995
		MX 9205824 A	01-04-1993
		NO 941280 A	08-04-1994
		PT 100943 A,B	29-10-1993
		SG 46599 A	20-02-1998
		WO 9307115 A	15-04-1993
		ZA 9207793 A	11-04-1994
WO 9206968 A	30-04-1992	US 5103024 A	07-04-1992
		AT 118772 T	15-03-1995
		AU 646311 B	17-02-1994
		AU 8848091 A	20-05-1992
		CA 2092997 A	18-04-1992
		CZ 282922 B	12-11-1997
		CZ 9701245 A	17-12-1997
		CZ 9701246 A	17-12-1997
		CZ 9701247 A	17-12-1997
		CZ 9502094 A	17-12-1997
		CZ 9300614 A	16-02-1994
		DE 69107622 D	30-03-1995
		DE 69107622 T	06-07-1995
		DK 553213 T	17-07-1995
		EP 0553213 A	04-08-1993
		ES 2070519 T	01-06-1995
		FI 931680 A	14-04-1993
		HK 1005026 A	18-12-1998
		HU 64049 A	29-11-1993
		HU 213731 B	29-09-1997
		IE 62940 B	08-03-1995
		JP 6502162 T	10-03-1994
		KR 166385 B	15-01-1999
		NO 301588 B	17-11-1997
		PT 99244 A,B	30-09-1992
		RU 2067580 C	10-10-1996
		SK 33993 A	06-10-1993
		US 5248793 A	28-09-1993
EP 0330172 A	30-08-1989	US 5003080 A	26-03-1991
		AT 109777 T	15-08-1994
		AU 634689 B	25-02-1993
		AU 1601792 A	09-07-1992
		AU 635171 B	11-03-1993
		AU 1601892 A	09-07-1992
		AU 3349689 A	06-09-1989
		CA 1330441 A	28-06-1994
		DE 68917336 D	15-09-1994
		DE 68917336 T	01-12-1994
		DK 197090 A	04-10-1990
		EP 0448552 A	02-10-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HK/00042

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0330172 A		ES 2058356 T FI 94958 B FI 941550 A,B, HK 1000732 A IE 63994 B JP 3009139 B JP 10195071 A JP 2843627 B JP 3502798 T KR 9711578 B KR 9711579 B KR 123813 B KR 9711462 B KR 137884 B NO 177566 B NO 941725 A,B, NO 943057 A,B, NO 951075 A,B, NO 963245 A NZ 228050 A NZ 238843 A NZ 238844 A NZ 238845 A PT 89774 A,B US 5245047 A US 5280126 A WO 8907598 A US 5124482 A US 5149837 A US 5216174 A ZA 8900989 A US 5097045 A	01-11-1994 15-08-1995 05-04-1994 24-04-1998 28-06-1995 14-02-2000 28-07-1998 06-01-1999 27-06-1991 12-07-1997 12-07-1997 27-11-1997 11-07-1997 01-05-1998 03-07-1995 27-09-1990 27-09-1990 27-09-1990 27-09-1990 29-01-1992 29-01-1992 29-01-1992 29-01-1992 04-10-1989 14-09-1993 18-01-1994 24-08-1989 23-06-1992 22-09-1992 01-06-1993 31-10-1990 17-03-1992
US 5599954 A	04-02-1997	JP 8198832 A	06-08-1996
WO 9804543 A	05-02-1998	AU 3515497 A EP 0915866 A HU 9904348 A US 5998633 A	20-02-1998 19-05-1999 28-04-2000 07-12-1999
WO 9957109 A	11-11-1999	NONE	
US 5278313 A	11-01-1994	US 5457227 A US 5594153 A	10-10-1995 14-01-1997